Cardiac Angiotensin AT₂ Receptor
What Exactly Does It Do?

George W. Booz

Angiotensin II (Ang II) has multiple actions in the heart that affect cardiac remodeling and contractility, most of which can be attributed to activation of the Ang II type-1 (AT₁) receptor.¹ This 7-transmembrane-domain, G-protein-coupled receptor activates multiple intracellular signaling pathways that encompass calcium, phospholipids, kinases, and reactive oxygen species. But cardiac cells also express a second major Ang II membrane receptor, namely type-2 (AT₂), which despite being cloned more than a decade ago, remains something of an enigma as far as what function it plays in normal or diseased hearts.² AT₁ and AT₂ exhibit only ≈30% primary sequence homology, but both belong to the class A rhodopsin-like family of G-protein-coupled receptors and have similar high affinities for Ang II in the nanomolar range. However, the similarity ends there. The 2 receptors differ in which heterotrimeric G-proteins they activate. In contrast to AT₁, only 4 major signaling mechanisms have been linked to AT₂: activation of protein phosphatases and protein dephosphorylation, regulation of the bradykinin-nitric-oxide-cGMP system, activation of phospholipase A₂ (PLA₂) and arachidonic acid release, and sphingolipid-derived ceramide formation.³ Which mechanism predominates appears to be cell-type specific.

Because AT₂ couples to phosphatase activation whereas AT₁ activates various kinases, it is not surprising that in a variety of cell types the 2 receptors appear to be mutually antagonistic. In the early 1990s there were many reports demonstrating that Ang II has growth-promoting effects on cardiac cells via AT₁ activation, and some of the early reports for an antagonistic relationship between the 2 receptors demonstrated that AT₂ is growth inhibitory. Early studies found that AT₂ opposes the hypertrophic action of AT₁ on cultured rat cardiac myocytes.³,⁴ Shortly thereafter, Bartunek et al. were able to show, using the perfused hypertrophied adult rat heart, that inhibition of AT₂ amplifies the immediate growth response of the left ventricle to Ang II.⁵ Their findings are complemented by a recent study showing that AT₂ blockade diminishes the antihypertrophic effects of AT₁ receptor blockade in an adult rat model of pressure-overload cardiac hypertrophy.⁶ However, these studies used receptor blockers, and not all such studies found evidence for an antagonistic relationship between AT₁ and AT₂ on cardiac hypertrophy.⁷ Results using AT₂ knockout mice have made matters more confusing, with studies involving different in vivo models of cardiac remodeling reporting no,⁷ suppressive,⁸ or obligatory⁹ role for AT₂ in the development of pathological hypertrophy.

How is it possible to reconcile these disparate findings? As suggested by Schneider and Lorell,¹⁰ AT₂ function is likely to be context-specific. In other words, the response of a particular cell or tissue to Ang II will be reflective of the ratio of AT₁ to AT₂ at any particular time, which is not static, but changes in the diseased heart. In the hypertrophied rat heart, the ratio of AT₂ to AT₁ is increased, which could explain why in the above cited study by Bartunek et al inhibition of AT₂ did not amplify the growth response to Ang II in normal rat hearts. In failing human hearts, AT₁ levels in the ventricles are decreased, whereas AT₂ expression is either unchanged or increased; in the ventricles of patients with end-stage ischemic heart disease or dilated cardiomyopathy, AT₂ levels are increased in endocardial, interstitial, and infracted regions compared with the noninfarcted myocardium.² Furthermore, whereas AT₁ is the predominant Ang II receptor in animal hearts, studies indicate either that AT₂ predominates in the human heart or that AT₁ and AT₂ are present in nearly equal proportion.²,¹¹ Thus, context (ie, the AT₁/AT₂ ratio) is an especially important consideration when extrapolating from results obtained with animal models to humans.

The assessment that “context is everything” for resolving the pathophysiological function of AT₂ gives added importance to the study by Alfakih et al. that appears in this issue of Hypertension. In a prospective study involving 197 patients with systemic hypertension and 60 normal volunteers, these investigators evaluated whether there was an association between a common intronic polymorphism (−1332 G/A) of the AT₂ gene and left ventricular hypertrophy. The AT₂ gene has 3 exons and 2 introns, with the entire reading frame for AT₂ located on exon 3. The polymorphism site is located 29 bp before exon 2, close to a region important for transcriptional activity. Persons with the G allele have exon 2 missing and less effective transcription of the AT₂ gene. The authors observed a statistical association between the AT₂ (−1332 G) allele and the presence of left ventricular hypertrophy in patients with hypertension, despite the fact that the majority

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of patients were on antihypertensive medications. Thus, the findings of this study are in keeping with the hypothesis that AT2 has antigrowth effects on the heart that counterbalance the growth-promoting effects of AT1. In addition, as noted by the authors, the AT2 polymorphism might serve as a marker for patients who would benefit more from blockade of the AT1 receptor.

One premise of the conclusion reached by Alfakih et al is that the function of AT2 is revealed only under a stress condition, meaning that reduced AT2 expression during development itself did not set into play some event that results in a greater propensity for cardiac hypertrophy with hypertension. If so, then their study by design defines a role for the cardiac AT2 receptor in the human heart strictly in context. Of course their study cannot address the issue of whether AT2 activation has a direct effect on cardiac myocytes that impacts on growth. In fact, the cellular distribution of AT2 in the human heart is still unsettled, although several studies have identified AT2 in human cardiac myocytes. Moreover, even if AT2 does oppose the growth-promoting effects of AT1 at the level of the cardiac myocyte, the mechanism by which it does so may turn out to be more complicated than originally envisioned. Besides activating potentially antagonistic signaling pathways, AT2 could perhaps modulate AT1 function through a direct interaction, and vice versa. If this hypothesis is correct, then labeling AT2 antigrowth and AT1 pro-growth would certainly be overly simplistic. An entirely different response to AT2 activation might be seen at one ratio of AT1 to AT2 compared with another. Thus, the recent findings of Lorell and colleagues that targeted overexpression of AT2 to the ventricles leads to dilated cardiomyopathy with an increase in the size of myocytes and heart failure cannot be construed as being at odds with the findings of Alfakih et al. Finally, one issue not addressed by Alfakih in their discussion is the possibility that reduced AT2 expression in their patients may have been accompanied by an increase in AT1 expression and what impact that might have had on the level of cardiac hypertrophy. Others have noted an increase in left ventricular AT1 expression in AT2 knockout mice. Perhaps AT2 counterbalances the actions of AT1 by impacting on its level of expression.

Evidence indicates that AT2 is also involved in cardiac fibrosis and electrical remodeling. There again, understanding the pathophysiological role that AT2 plays will require a consideration of the level of interplay between AT1 and AT2. Undoubtedly, as with cardiac growth, any answer to the question of what role AT2 plays in these processes will need to be prefaced with the words “that depends.”

References
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